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Pediatric first time non-febrile seizure with focal manifestations: Is emergent imaging indicated?

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ABSTRACT

Purpose: To assess the prevalence of clinically urgent intra-cranial pathology among children who had imaging for a first episode of non-febrile seizure with focal manifestations.
Methods: We performed a cross sectional study of all children age 1 month to 18 years evaluated for first episode of non-febrile seizure with focal manifestations and having neuroimaging performed within 24 h of presentation at a single pediatric ED between 1995 and 2012. We excluded intubated patients, those with known structural brain abnormality and trauma. A single neuro-radiologist reviewed all cranial computed tomography and/or magnetic resonance imaging performed. We defined clinically urgent intracranial pathology as any finding resulting in a change of initial patient management. We performed univariate analysis using χ^2 analysis for categorical data and Mann–Whitney *U* test for continuous data.
Results: We identified 319 patients having a median age of 4.6 years [IQR 1.8–9.4] of which 45% were female. Two hundred sixty-two children had a CT scan, 15 had an MR and 42 had both. Clinically urgent intra-cranial pathology was identified on imaging of 13 patients (4.1%; 95% CI: 2.2, 7.0). Infarction, hemorrhage and thrombosis were most common (9/13). Twelve of 13 were evident on CT scan. Persistent Todd's paresis and age $\leq$18 months were predictors of clinically urgent intracranial pathology. Absence of secondary generalization and multiple seizures on presentation were not predictive.
Conclusions: Four percent of children imaged with first time, afebrile focal seizures have findings important to initial management. Children younger than $\leq$18 months are at increased risk.
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1. Introduction

Pediatric seizures are a common problem. A large proportion of all pediatric seizures occur among children younger than 2 years of age[1,2] where seizures tend to be of shorter duration and in more than 50% have focal features.[3–6] Previous literature suggests that nearly half of children presenting with seizure having focal manifestations will have abnormal neuroimaging. While useful to help identify seizure etiology few of these findings lead to an acute change in management.[6,7] Clinicians must determine whether to perform neuroimaging urgently with CT or MR or whether imaging can be done electively or not at all. The focus of this paper will be on the rate of neuroimaging findings that can be expected to result in an acute change in management or what we describe as clinically urgent intra-cranial pathology and whether current imaging recommendations can be refined.

In 2009, the international League Against Epilepsy (ILAE) published imaging guidelines for new onset epilepsy,[8] offering a five point scale classification of neuroimaging findings, presented in Table 1. While not aimed at first time seizure per se, this neuroimaging classification is relevant to assessing the results of emergent imaging

Young children appear more likely to have findings on emergent neuroimaging that will alter the acute medical or surgical management,[5,9] with one study reporting a prevalence of 17% among children younger than 33 months[9] compared to an estimated 2–4% overall.

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Table 1
Classification of neuroimaging results.

Abnormality	Definition	Examples
(1) Non-specific	Lesions not requiring immediate intervention that may be responsible for seizure	Periventricular leukomalacia, generalized cerebral atrophy
(2) Static-remote	Non-progressive lesions of the CNS that occurred remotely in time	Porencephaly, other malformations of cortical development
(3) Focal	Focal lesions responsible for seizure but not requiring immediate intervention	Focal cortical dysplasia, mesial temporal sclerosis
(4) Sub-acute or chronic[a]	Process responsible for seizure that does not require immediate intervention but has important therapeutic or prognostic implications	Brain tumor or mass, adrenoleukodystrophy
(5) Emergent[a]	Acute process requiring immediate, urgent intervention[a]	Ischemic stroke, cerebral hemorrhage, hydrocephalus, encephalitis, meningitis, metabolic cytopathy, cerebral edema, acute cerebral herniation, skull fracture with bleed, new hypoxic injury

[a] Referred to in our manuscript as clinically significant intra-cranial pathology.

Guidelines regarding neuro-imaging for the evaluation of a child with a first episode of non-febrile seizure have also been published by the American Academy of Neurology (AAN), the Child Neurology Society (CNS), and the American Epilepsy Society (AES).[10] These guidelines call for emergent neuroimaging for children with persistent post-ictal neurologic deficit and children that are not back to baseline neurologic status within a few hours. Children with focal manifestations and age <1 year are candidates for non-emergent MR neuroimaging.[10] We sought to identify a selected group of children over 1 month of age presenting with a first-time non-febrile seizure with focal manifestations that would most benefit from emergent neuroimaging while also determining the prevalence of clinically urgent intra-cranial pathology among these children.

2. Methods

2.1. Study design and setting

This is a cross sectional study of all patients 1 month to 18 years of age presenting to an urban pediatric tertiary care ED between October 1995 and March 2012 with a first-time non-febrile seizure with focal manifestations. This ED serves approximately 55,000 children per year. The study was approved by the hospital institutional review board.

2.2. Patient identification

Patient identification was performed using a computer assisted screening tool using regular expressions.[11] This technique is similar to key word search tools, but provides a more comprehensive search allowing inclusion of possible misspelled and mistyped variations of the key words of interest. This was followed by manual chart review of patients identified by the screening tool. The authors have previously utilized this method to significantly enhance case detection compared to the use of ICD-9 coding.[12–14]

2.3. Patient population

We included all children evaluated in the ED with a first-time non-febrile seizure with focal manifestations, who underwent neuroimaging within 24 h of ED presentation. We excluded children with altered mental status, acute trauma, inability to assess focal neurologic signs (e.g., intubated patients or pre-existing hemiparesis), or a pre-existing and known neurologic abnormality such as structural brain abnormalities (preexisting tumor, stroke, hydrocephalus, arterio venous malformation [AVM], presence of a ventriculo-pertoneal [VP] shunt, tuberous sclerosis).

Focal manifestations were defined as any recorded transitory disturbance in motor function with focality such as eye deviation, head tilt, or isolated limb twitching. Patients were also considered to have focal manifestations if a Todd's paresis was noted following what would otherwise have appeared to be a generalized seizure. Focal manifestations, number and duration of seizure(s) were based on history in the medical record from any witnesses.

2.4. Data collection

The review followed the principles described by Gilbert et al.[15] including selection of participants, definition of variables, use of abstract forms to train data abstractors (all physicians), meeting regularly to assess disagreements and disputes and assessment of inter-reviewer agreement rates. Two study investigators (N.A. and A.K.) reviewed the complete hospital medical records from the time of index visit to the time of chart review for all study patients. The following factors were abstracted: age, gender, prior history of seizures, seizure characteristics, neurologic examination findings, radiologic results, seizure management and ED disposition. Laboratory databases were reviewed for laboratory studies including chemistries, toxicology studies and cerebrospinal fluid studies if performed. Records were also screened for delayed imaging results (obtained greater than 24 h after presentation) and outpatient follow up with a neurologist. In cases where clinician records differed, we abstracted data from the documentation of the most senior clinician. Findings were considered missing if not documented by any treating clinician.

2.5. Classification of neuro-imaging studies

A single neuro-radiologist (SPP), blinded to clinical history and patient outcome, reviewed all neuroimaging studies (cranial computed tomography or magnetic resonance imaging) performed within 72 h of initial presentation to the study site ED. The study radiologist's interpretation was used for all analyses.

2.6. Outcome measure

Our primary outcome was *clinically urgent intracranial pathology* on neuroimaging defined as any finding likely to result in a medical or surgical intervention. These findings include: any mass lesion causing mass effect, infarction, hemorrhage, arterio-venous malformation (AVM), hydrocephalus, abscess, or acute disseminated encephalomyelitis (ADEM). Our outcome measure corresponds with level 5 of the ILAE scale (Table 1).

Findings such as mild ventricular asymmetry, suspected pre-existing hydrocephalus, small non-obstructive tumors, or an increase in the extra-axial fluid space were not considered urgent

neuroimaging intracranial pathology. The finding a structural abnormality without mass effect may result in the use of an anti-epileptic medication but this was not considered an emergent change in management.

2.7. Kappa analysis for clinical predictors

A pediatric neurologist (AT) reviewed the medical records of a randomly selected 15% of the study patients and abstracted clinical data. For each candidate predictor, we calculated both percent agreement and the kappa statistic to assess inter-rater reliability of candidate predictor.[16] We considered clinical predictors with a lower end of the 95% confidence interval (CI > 0.4) to have moderate agreement.

2.8. Statistical analysis

Candidate clinical predictors were evaluated for their potential correlation with the eventual abnormality on neuroimaging. We performed univariate analysis using χ^2 analysis for categorical data and Mann–Whitney *U* test for continuous data.

We conducted a secondary analysis on patients who had no criteria for emergent imaging per current guidelines (e.g., no Todd's paresis). We used the Statistical Program for the Social Sciences (IBM SPSS Statistic Version 21, IMB Inc., Chicago, IL).

3. Results

Three hundred nineteen children met inclusion criteria for first time non-febrile seizure with focal manifestations and imaging within 24 h of presentation. See Fig. 1 for case identification.

The median patient age was 4.6 years [IQR 1.8–9.4] and 143 (45%) were females. One hundred seventy-eight children (56%) were admitted to the hospital. All patients (n = 319) had initial neuroimaging studies performed while in the ED. The emergent neuroimaging modality utilized was as follows: 262 children had a CT scan, 42 patients had both a CT and MR, and 15 had MR alone during the initial visit. One hundred sixty-three (62%) had a

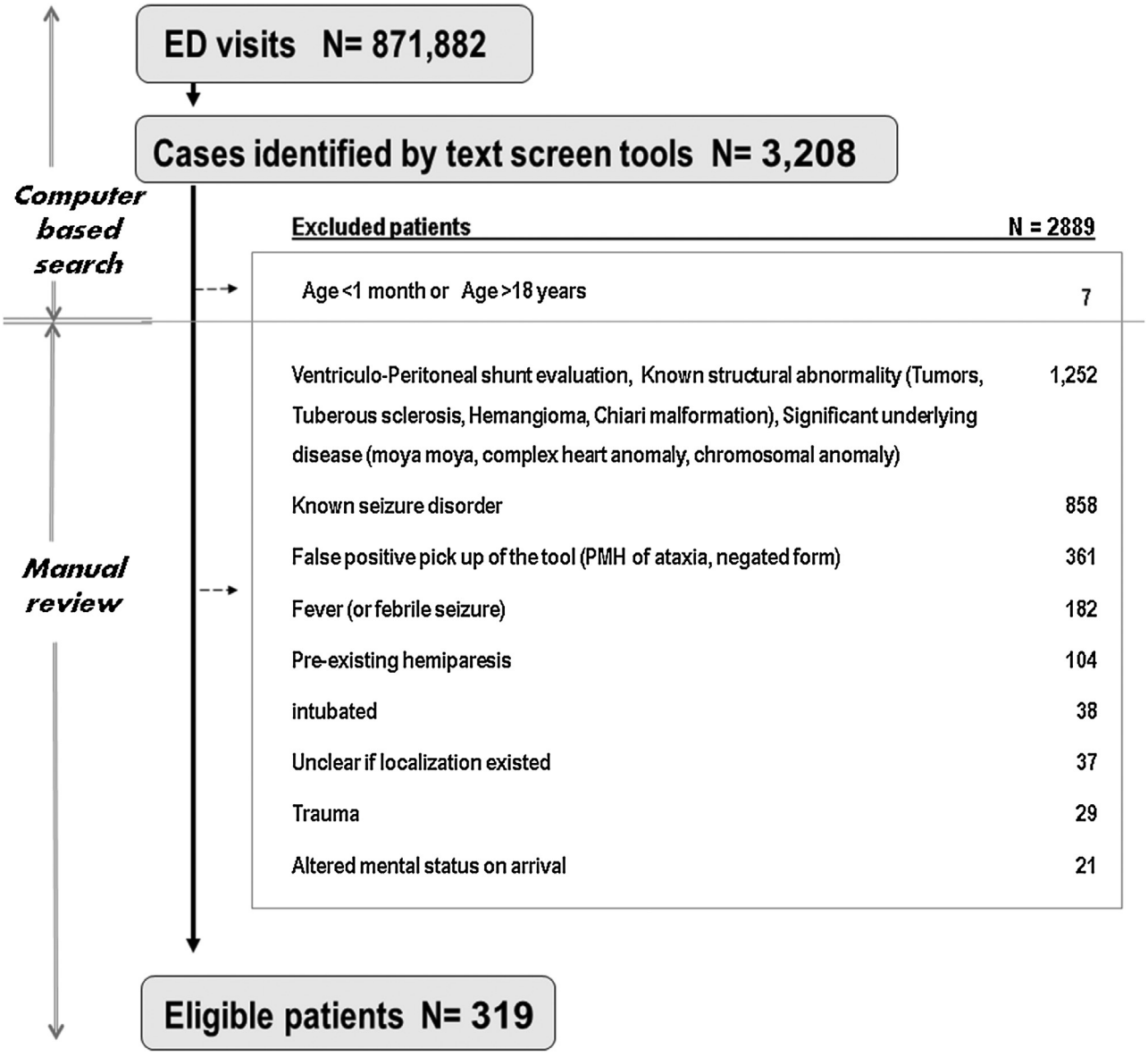

Fig. 1. Case identification.

subsequent MR done within our institution of which 33% were done within 72 h of presentation. The median time to follow-up MR was 11 days [IQR 2–46]. One hundred forty-five children (46%) were transferred to our ED from another facility of which 110 (76%) had a brain CT prior to transfer.

Thirteen of the 319 children had a finding of clinically urgent intracranial pathology (4.1%; 95% CI: 2.2, 7.0). Hemorrhage and infarction were most common (5 and 4 cases, respectively). One patient had clinically urgent intra-cranial pathology on a subsequent MR that was not identified on CT. The prevalence of clinically urgent intracranial pathology was the same among patients presenting primarily to our facility (7/174; 4%; 95% CI: 1.8, 10) as seen among those seen initially at an outside facility (6/145; 4.1%; 95% CI: 1.7, 9.2%).

Brief summaries of patient presentations for those with significant urgent neuroimaging findings are presented in Table 2.

Patient characteristics with and without clinically urgent intracranial pathology are presented in Table 3. A sub-analysis excluding patients with Todd's paresis is presented in the bottom portion of the table.

Fig. 2 presents a 2×2 table for applying existing imaging guidelines and adding an age <18 months as part of imaging recommendation.

3.1. Results of delayed non-emergent MR neuroimaging

Two hundred five children of 252 who had CT scan for their urgent imaging, had a subsequent MR. Of these, 58/205 (28.2%) had abnormal findings on neuro-imaging. Using the ILAE imaging classification, one patient (0.5%) had a category 5 finding, nine patients (4.4%) level 4, 18 patients (8.8%) each in levels 3 and 2, and 12 patients (5.8%) were category 1. Of these 58 patients with findings 17 (29%) were not seen on the initial CT including one patient with a category 5 finding (which was of non-symmetric subcortical white matter signal abnormalities predominantly in the bilateral frontal lobes with leptomeningeal enhancement later confirmed by LP to be meningo-encephalitis).

4. Discussion

We present a large retrospective cohort of children with first time non-febrile seizure with focal manifestations for whom imaging could be done urgently or non-urgently by existing guidelines. In our cohort, the proportion of children with clinically urgent intracranial pathology (4.1%) was lower than previously reported.[5,9] Further we confirm that children less than 18 months of age and those with Todd's paresis may be at higher risk of having clinically urgent intra-cranial pathology.

Two large prior studies describe a higher prevalence of clinically urgent intra-cranial pathology among similar children. These studies included neuroimaging findings matching an ILAE category of 4 or 5, whereas for the objective to specifically determine which patients benefit from emergent imaging we include only those which most closely match to a category 5 finding. For example, brain mass with no associated hydrocephalus or mass effect was not considered to require emergent intervention in our cohort. Despite the difference in definitions it is useful to note that Garvey et al. performed a retrospective analysis of children who presented with a first time seizure[17] with a subset of 37 children for whom the seizure had documented focal onset. CT scan abnormalities were identified in 11 (37%) of these children with findings requiring intervention in 5 (13.5%). Sharma et al. reviewed children with new onset seizure of whom 133 presented with documented focal features.[9] Seventeen patients (13%) had imaging findings that lead to a change in management.

Current imaging guidelines aimed at first time non-febrile seizures do not distinguish those presenting with focal and non-focal manifestations. These guidelines have identified persistent

Table 2
Clinically urgent intra-cranial pathology.

	Age and gender	Presentation	Imaging category	Imaging results
1	4m M	Episodes of unilateral leg jerks	Bleed	Acute right parietal intra-parenchymal hemorrhage with additional hemorrhage noted along the inter-hemispheric fissure and tracking along the tentorium
2	6m M	Unilateral upper and lower limb twitching followed by Todd's paresis	Bleed	An intermediate density subdural fluid collection overlying the left frontal lobe
3	2m F	Right sided tonic clonic seizure	Bleed	Subdural and subarachnoid hemorrhage. Unenhanced CT findings concerning for cerebral edema. Focal left parietal hypodensity. Final diagnosis – non accidental trauma
4	6.5 F	Clonic movements of the right upper extremity, Todd's paresis	Bleed/mass	Left basal ganglia bleed, cavernous malformation in the left basal ganglionic/frontal regions. Multiple cavernous malformations in the supratentorial and infratentorial parenchyma
5	11m M	Unilateral tonic clonic seizure followed by atonic phase and then Todd's paresis	Bleed	Left hemisphere subdural hematoma
6	14.5y F	Left sided focal seizure involving face and neck	Mass	Right frontal lobe mass with imaging appearance most suggestive of a high grade glial neoplasm or pleomorphic xanthoastrocytoma
7	13m F	Left eye deviation, vomiting	Mass	Large, calcified posterior fossa mass, effacement of the fourth ventricle and moderate hydrocephalus
8	4.5m M	Unilateral facial twitching and eye deviation, reoccurring three times	Infarct	Right MCA infarct
9	6m M	Left sided lip twitching and left arm stiffening	Infarct	Several ill-defined low density areas involving the right cerebral hemisphere
10	5y M	Right sided tonic seizure of the arm and leg followed by Todd's paresis	Infarct, thrombosis	Venous thrombosis of the internal cerebral veins, vein of Galen, straight sinus and partial thrombosis of the bilateral medial third of the transverse sinuses with associated left thalamic venous ischemia
11	6y F	Unilateral tonic-clonic seizure with eye deviation	Infarct	Multiple calcifications and concern for new multifocal infarcts
12	4.5 F	Left eye deviation	Infectious	Non-symmetric subcortical white matter signal abnormalities predominantly in the bilateral frontal lobes with leptomeningeal enhancement. Findings may be seen with infection (meningitis, meningoencephalitis) – confirmed by LP
13	16y M	Multiple short episodes of right hand shaking followed by a 2 min GTC seizure	Vasculitis	Nonspecific abnormalities consistent with meningoencephalitis or vasculitis

Table 3
Patient characteristics.

Characteristics All children	Clinically urgent intra-cranial pathology ($N=13$)	No clinically urgent intra-cranial pathology ($N=306$)	Significance
Demographics			
Gender: Female	7/13 (54%)	136/306 (44)	$P=0.58$
Age younger than 18 months	6/13 (46%)	66/306 (22%)	$P=0.08$
History			
Multiple seizures on presentation	2/13 (15%)	124/306 (40%)	$P=0.09$
Secondary generalization	2/13 (15%)	78/306 (26%)	$P=0.5$
Physical exam			
Todd's paresis	4/13 (31%)	14/306 (5%)	$P=0.004$
Characteristics Excluding Todd's paresis	Positive emergent imaging findings ($N=9$)	Negative emergent imaging findings ($N=292$)	Significance
Demographics			
Gender: Female	6/9 (67%)	130/292 (44%)	$P=0.31$
Age younger than 18 months	5/9 (56%)	64/292 (22%)	$P=0.03$
History			
Multiple seizures on presentation	2/9 (22%)	118/292 (40%)	$P=0.33$
Secondary generalization	2/9 (22%)	75/292 (26%)	$P=1.00$

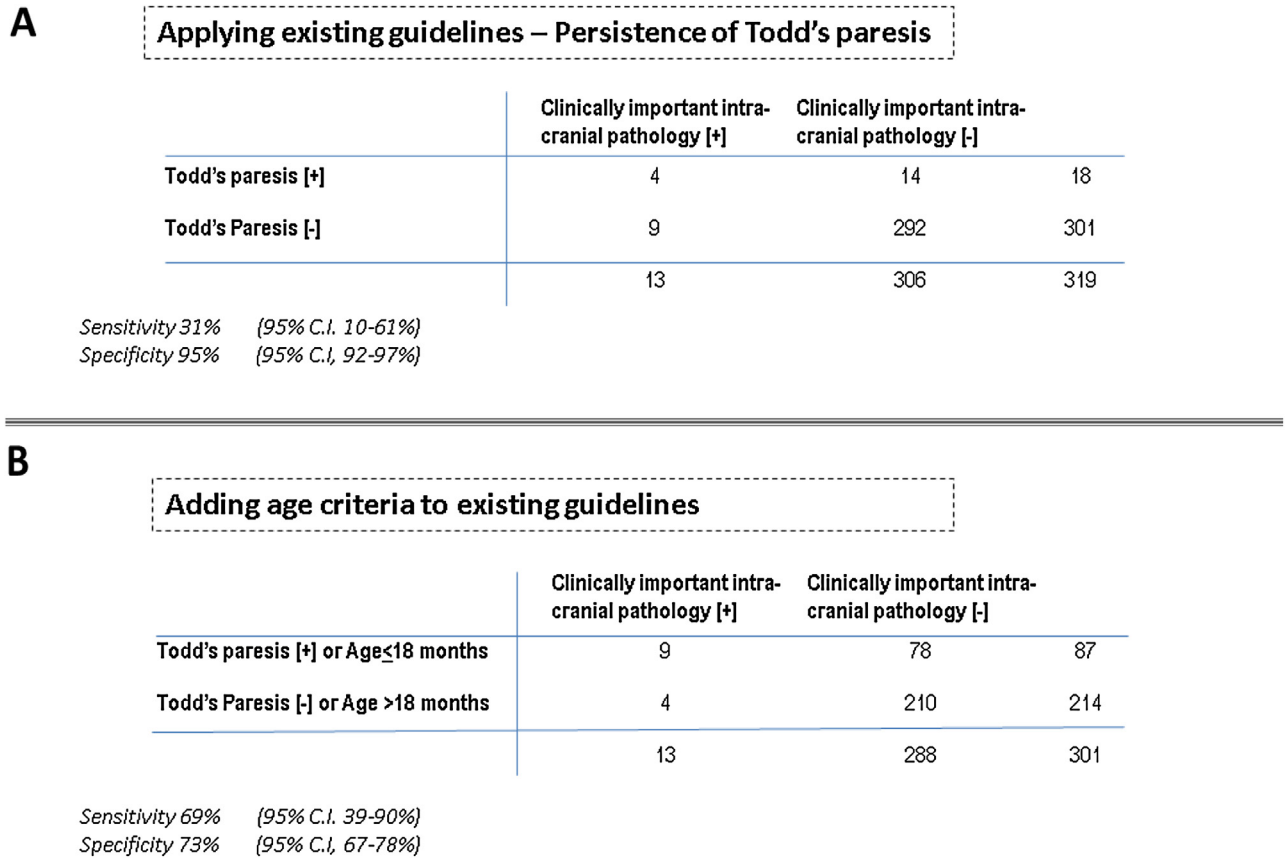

Fig. 2. Performance of current imaging guidelines and addition of an age cut off.

Todd's paresis and persistent abnormal mental status as risk factors.[10] We sought to further refine the clinical decision making by removing patients with ongoing status epilepticus, altered mental status or signs of elevated intracranial pressure in order to determine what other patient groups should have emergent imaging. We decided to include patients with apparent Todd's paresis as there is less clinical agreement on the need for emergent imaging. Our data confirms the reports of Ferry[18] and Vining[19] and others that children with focal neurologic deficits that do not return to baseline within a few hours are at significantly increased risk of having a significant emergent neuroimaging finding. Unfortunately this finding has poor sensitivity as the presence of Todd's paresis will not identify 70% of the cases with clinically urgent intra-cranial pathology seen in our cohort. We recommend adding age less than 18 months as an additional indication for emergent imaging as this resulted in the identification of an additional 40% of the cases in our cohort. Our data identify children less than 18 months of age to have an 8% risk of clinically urgent intracranial pathology compared to 4% overall. Young age has previously been associated with seizure focal manifestations[20] and high rates of imaging findings.[5] Sharma

et al. reported rates of imaging findings of 13% for all children and 29% for children younger than 33 months of age.

Conversely children with first time non-febrile seizure with focal manifestations who are greater than 18 months of age and do not have Todd's paresis, abnormal mental status, signs of elevated ICP or status epilepticus are at a much lower risk of clinically urgent neuroimaging findings (1.8% in our cohort).

Our study has several important limitations. First, our study was retrospective and the predictors were assessed by medical chart review. We attempted to minimize this potential bias by selecting objective parameters that would be recorded accurately in the medical chart with good inter-rater reliability for inclusion. Second, while our overall rate of significant emergent neuroimaging findings of 4.1% is lower than previously reported we believe we may overestimate the risk because we included only patients who were imaged. Third, seizure focality may be under reported by parents, bystander witnesses and clinicians and there is data suggesting inter-observer agreement on focal manifestations may be poor.[2] In addition focality is so common in infants that Korff et al.[20] titled their manuscript "Do generalized tonic-clonic seizures in infancy exist?". There is however data supporting the value of focality as a predictor in young children: Sharma et al.[9] showed a clear difference in imaging yield between children with generalized seizure on presentation and infants and toddlers with focal features.

Finally, despite the large number of patient in our study the number with urgent neuroimaging findings was too small to generate a multivariate model and a robust prediction rule. A larger study may allow further risk stratification for children and allow age-based subgroup analysis.

5. Conclusion

We identified a large retrospective cohort of children with first time non-febrile seizure with focal manifestations evaluated in the ED of a single center over an 18-year period with a 4% prevalence of clinically urgent intracranial pathology. Based on our data we suggest children less than 18 months should be considered for addition to imaging guidelines as an indication for emergent neuroimaging.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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